S100A9

S100 calcium-binding protein A9 (S100A9) also known as migration inhibitory factor-related protein 14 (MRP14) or calgranulin B is a protein that in humans is encoded by the S100A9 gene.

The proteins S100A8 and S100A9 form a heterodimer called calprotectin.

S100-A9 is a member of the S100 family of proteins containing 2 EF hand calcium-binding motifs. S100 proteins are localized in the cytoplasm and/or nucleus of a wide range of cells, and involved in the regulation of a number of cellular processes such as cell cycle progression and differentiation. S100 genes include at least 13 members which are located as a cluster on chromosome 1q21. This protein may function in the inhibition of casein kinase.

MRP14 complexes with MRP-8 (S100A8), another member of the S100 family of calcium-modulated proteins; together, MRP8 and MRP14 regulate myeloid cell function by binding to Toll-like receptor 4 (TLR4) and the receptor for advanced glycation end products.

The inflammatory responses to surgical brain injury (SBI) were associated with infiltration of S100A9-expressing myeloid-derived cells into the brain. Local release of pro-inflammatory S100A9 was confirmed in patients following tumor resection. RAGE and S100A9 inhibitors were as effective as dexamethasone in attenuating neuroinflammation. However, unlike dexamethasone and S100A9 inhibitor, RAGE inhibition did not diminish the efficacy of anti-PD-1 immunotherapy in glioma-bearing mice. These observations confirm the role of the RAGE axis in surgically induced neuroinflammation and provide an alternative therapeutic option to dexamethasone in managing post-operative brain edema [1)].

S100A9 protein enhances tumor progression. A study firstly demonstrated that both intracellular and extracellular S100A9 promoted the expression of Vimentin and Intercellular cell adhesion molecule-1 (ICAM-1), coupled with reduced E-cadherin in PA. As a result, PA acquired the phenotype of Epithelial-Mesenchymal Transition (EMT), leading to proliferation, cell cycle progression, migration and invasion. In addition, we indicated S100A9-induced EMT was mediated by activation of AKT1. Furthermore, immunohistochemistry showed that S100A9 expression was higher in invasive PA than that in non-invasive PA. These data extended our understanding for the effects of S100A9 on PA invasion and contributed to further development of a promising therapeutic target for invasive PA [2)].

The S100A9-driven amyloid-neuroinflammatory cascade occurring during primary and secondary TBI events can serve as a mechanistic link between TBI and Alzheimer's as demonstrated recently in the human brain tissues. Here by using immunohistochemistry in the controlled cortical impact TBI mouse model we have found pro-inflammatory S100A9 in the brain tissues of all mice on the first and third post-TBI days, while 70% of mice did not show any S100A9 presence on seventh post-TBI day similar to controls. This indicates that defensive mechanisms effectively cleared S100A9 in these mouse brain tissues during post-TBI recovery. By using sequential immunohistochemistry we have shown that S100A9 was produced by both neuronal and microglial cells. However, Aβ peptide deposits characteristic for Alzheimer's disease were not detected in any post-TBI animals. On the first and third

post-TBI days S100A9 was found to aggregate intracellularly into amyloid oligomers, similar to what was previously observed in human TBI tissues. Complementary, by using Rayleigh scatting, intrinsic fluorescence and atomic force microscopy we demonstrated that in vitro S100A9 self-assembles into amyloid oligomers within minutes. Its amyloid aggregation is highly dependent on changes of environmental conditions such as variation of calcium levels, pH, temperature and reduction/oxidation, which might be relevant to perturbation of cellular and tissues homeostasis under TBI. Present results demonstrate that S100A9 induction mechanisms in TBI are similar in mice and humans, emphasizing that S100A9 is an important marker of brain injury and therefore can be a potential therapeutic target [3].

The expression level of S100A9 was fivefold higher in glioma stem cells than differentiated cells. Similar results were also observed in glioma stem cells derived from other glioma cells. More importantly, knockdown of S100A9 by RNA interference suppressed the proliferation of glioma stem cell line and decreased the growth of xenograft tumors in vivo. Taken together, these results indicate that the tumorigenesis potential of CSCs arises from highly expressed S100A9 [4].

1)
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